This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[MA179 trade name][*]
Manufacturer of Prequalified Product	Guilin Pharmaceutical Co., Ltd Oral Solid Dosage Workshop I No. 43, Qilidian Road, Guilin 541004 Guangxi, China.
Active Pharmaceutical Ingredient(s) (API)	Pyrimethamine, sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarial, Pyrimethamine combinations (P01BD51)
Therapeutic indication	[MA179 trade name] is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas. [MA179 trade name] is also indicated for perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission, where sulfadoxine-pyrimethamine is effective.

1. Introduction

[MA179 trade name] is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas.

[MA179 trade name] is also indicated for perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission, where sulfadoxine-pyrimethamine is effective. Moderate to high perennial malaria transmission settings are defined as areas with P. falciparum parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000.

[MA179 trade name] should ideally be administered as directly observed therapy (DOT).

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with [MA179 trade name]. Official guidance will normally include WHO (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf) and local health authorities' guidelines.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

Active pharmaceutical Ingredient (API)

Pyrimethamine and sulfadoxine have been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that these APIs, used in the manufacture of [MA179 trade name], are of good quality and manufactured in accordance with WHO good manufacturing practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include hypromellose, hyprolose, sucralose and magnesium stearate. None of the ingredients are from animal origin. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white round tablet, debossed with "SP" on one side and a break line on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered as supported by divisibility studies. The tablets are packed in a PVC-Alu blister card.

Two strengths of Pyrimethamine/Sulfadoxine dispersible tablets proportionally similar in composition were developed: 25mg/500mg and 12.5mg/250mg. The formulation development was first realized on the 25/500mg dispersible tablet and subsequently the formulation for the 12.5mg/250mg strength was obtained using dose-proportionality approach. The higher strength was used in the bioequivalence study against the WHO recommended comparator product, Fansidar® tablets (pyrimethamine/sulfadoxine 25mg/500mg).

The aim of the product development was to obtain a stable and robust formulation of pyrimethamine/sulfadoxine 25mg/500mg dispersible tablets. The selection of excipients was based on the physico-chemical characteristics of the APIs and the quality target product profile. Sucralose is included to mask the mildly bitter taste of sulfadoxine. The wet granulation method is used in manufacture of the tablets. The critical steps of the manufacturing process were optimized to obtain tablets of desired characteristics- including disintegration and dissolution. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification (HPLC and TLC), uniformity of dosage units (by content uniformity), fineness of dispersion, disintegration time (≤ 3min.), friability, dissolution (HPLC detection), loss on drying, related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at accelerated storage condition in the packaging proposed for marketing of the product. A slight increase in degradation products were observed, though these stayed well within the agreed

limits. Based on the available stability data the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2014 according to internationally accepted guidelines.

Study title:

A randomized, open label, balanced, one period, two treatment, single dose, parallel, truncated, bioequivalence study of FDC dispersible tablets of Sulfadoxine 500 mg and Pyrimethamine 25 mg of Guilin Pharmaceutical Co., Ltd., with Fansidar Sulfadoxine 500 mg and Pyrimethamine 25 mg tablets, manufactured by F. Hoffmann-La Roche Ltd. Basel, Switzerland in normal, healthy, adult, male and female human subjects under fasting condition (study no. ARL/13/487).

The objective of the study was to compare the bioavailability of the stated Pyrimethamine/Sulfadoxine 25/500 mg FDC dispersible tablet manufactured for/by Guilin Pharmaceutical Co., Ltd., China (test drug) with the reference formulation Fansidar® (pyrimethamine/sulfadoxine) tablets 25/500 mg (Hoffmann-La Roche Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, parallel study in healthy subjects under fasting conditions. Each subject was assigned to receive one of the following treatments in a randomized fashion:

Treatment T: Test – 1 dispersible tablet Pyrimethamine/Sulfadoxine 25/500 mg

(pyrimethamine 25 mg + sulfadoxine 500 mg)
Batch no.: SP131106

Treatment R: Reference – 1 tablet Fansidar® 25/500 mg

(pyrimethamine 25 mg + sulfadoxine 500 mg)

Batch no. Z0110

Serial blood samples (1 pre-dose sample and 19 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for pyrimethamine and sulfadoxine were analyzed using a validated LC-MS/MS methods. The limit of quantification was stated to be about 10 ng/ml for pyrimethamine and about 1208 ng/ml for sulfadoxine.

The study was performed with 32 participants; data generated from a total of 32 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for pyrimethamine and sulfadoxine as well as statistical results are summarised in the following tables:

Pyrimethamine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	3.84 ± 1.47	4.47 ± 1.77	–	–
C_{max} (ng/mL)	193 ± 29 (191)	178 ± 20 (177)	107.9	99.8 – 116.5
AUC_{0-72h} (ng·h/mL)	9922 ± 1238 (9852)	9323 ± 782 (9292)	106.0	99.6 – 112.9

Sulfadoxine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	4.16 ± 1.33	11.5 ± 15.1	–	–
C_{max} (µg/mL)	70.2 ± 9.2 (69.7)	65.5 ± 4.8 (65.3)	106.7	100.3 – 113.6
AUC_{0-72h} (µg·h/mL)	4125 ± 507 (4096)	3935 ± 212 (3930)	104.2	98.5 – 110.3

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding pyrimethamine and sulfadoxine. Accordingly, the test Pyrimethamine/Sulfadoxine 25/500 mg FDC dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Fansidar® 25/500 mg tablet (Hoffmann-La Roche Ltd.).

4. Summary of product safety and efficacy

[MA179 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [MA179 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Fansidar® 25/500 mg tablets (Hoffmann-La Roche Ltd) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA179 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [MA179 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA179 trade name] has been shown to be bioequivalent with Fansidar® 25/500 mg tablets (Hoffmann-La Roche Ltd).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA179 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [MA179 trade name] was acceptable for the following indication: ' intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas and treatment of perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission, where sulfadoxine-pyrimethamine is effective', and would allow inclusion of [MA179 trade name], manufactured at Guilin Pharmaceutical Co., Ltd, Oral Solid Dosage Workshop I, No. 43, Qilidian Road, Guilin 541004, Guangxi, China in the list of prequalified medicinal products.